RESEARCH PAPER

Resveratrol-Functionalized Nanoscaffolds in Anticancer Therapy: Current Status and Future Outlook

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Abstract

Resveratrol, a naturally occurring polyphenolic compound found in grapes, berries, and peanuts, has garnered significant attention for its potent anticancer properties, including anti-proliferative, pro-apoptotic, anti-inflammatory, and anti-angiogenic effects. However, its clinical utility is limited by poor bioavailability, rapid metabolism, and low aqueous solubility. To overcome these limitations, recent advancements have focused on integrating resveratrol into scaffold-based delivery systems, which offer sustained release, targeted delivery, and enhanced therapeutic efficacy. This review summarizes the current state of resveratrol-integrated scaffolds in cancer therapy, highlighting the design strategies, materials employed (such as hydrogels, nanofibers, and 3D-printed constructs), and their preclinical outcomes. Furthermore, we discuss the biological mechanisms through which these scaffolds exert antitumor effects, as well as the challenges related to scalability, biocompatibility, and regulatory approval. Finally, the paper explores emerging trends and future directions, including smart scaffolds responsive to tumour microenvironmental cues and combinatorial approaches with chemotherapeutics or immunomodulators. The integration of resveratrol into scaffold-based platforms holds considerable promise for advancing personalized and localized cancer therapies.

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Introduction

One of the leading causes of death globally, cancer is expected to continue to climb because of aging populations and changing lifestyles, with an estimated 10 million deaths in 2020 alone (1,2).

Despite considerable advancements in diagnostics and therapeutic interventions including surgery, chemotherapy, radiation, and immunotherapy numerous limitations such as systemic toxicity, multidrug resistance, and tumour recurrence hinder the efficacy of conventional cancer treatments (3,4). Therefore, there is an ever-growing demand for innovative, targeted, and biocompatible treatment strategies.

In this context, natural polyphenolic compounds, particularly resveratrol (3,5,4'-trihydroxy-trans-stilbene), have emerged as promising adjuvants or alternatives in oncological therapeutics. Resveratrol is a phytoalexin primarily found in grapes, berries, and peanuts, known for its potent antioxidant, anti-inflammatory, anti-proliferative, and pro-apoptotic effects (5–7). Several in vitro and in vivo studies have demonstrated resveratrol's efficacy in modulating multiple cancer hallmarks, including cell cycle regulation, angiogenesis inhibition, metastasis suppression, and immune modulation (8–10). However, the clinical translation of resveratrol has been severely constrained by its poor aqueous solubility, rapid metabolism, low systemic bioavailability, and instability under physiological conditions (11,12).

To address these pharmacokinetic and pharmacodynamic challenges, researchers have turned to biomaterial-based scaffolds for localized and sustained delivery of resveratrol. A controlled environment for drug release and mechanical support

are provided by scaffolds, which can be made of natural or synthetic polymers and provide a three-dimensional (3D) matrix that resembles the extracellular matrix (ECM) (13,14).

The integration of resveratrol into such scaffolds has shown promise in enhancing its therapeutic potential by enabling targeted delivery, reducing systemic toxicity, and improving drug residence time at tumour sites (15,16).

Advancement of tissue engineering, nanotechnology, and material science led to the development of multifunctional scaffolds such as hydrogels, electro spun nanofibers, cryogens, and porous matrices embedded with resveratrol for cancer therapy. These platforms can be engineered to incorporate stimuli-responsive elements (e.g., pH, redox, temperature sensitivity) and can be tailored to deliver combination therapies, thereby amplifying anti-tumour efficacy (17–19).

This review aims to provide a comprehensive and up-to-date account of resveratrol-integrated scaffolds in the context of cancer therapy. We explore the physicochemical challenges of resveratrol, various scaffold materials and fabrication strategies, research in vivo and in vitro demonstrating therapeutic outcomes, and the translational potential of these systems. Furthermore, we discuss current limitations, knowledge gaps, and future research directions required for clinical applicability.

Mechanisms of Resveratrol in Cancer Therapy

Resveratrol, a naturally occurring polyphenol found in grapes, berries, and peanuts, has demonstrated potent anticancer activity by modulating various molecular targets and signalling pathways associated with tumour initiation, progression, and metastasis. Its broad-spectrum efficacy arises from its multitargeted approach to regulating cancer hallmarks such as sustained proliferative signalling, evasion of apoptosis, angiogenesis, invasion, and inflammation.

1. Induction of Apoptosis and Cell Cycle Arrest

Resveratrol stimulates apoptosis in cells via extrinsic (death receptor-mediated) and intrinsic (mitochondrial-mediated) mechanisms. It causes cytochrome c release and caspase activation by upregulating pro-apoptotic proteins like Bax and downregulating anti-apoptotic proteins like Bcl-2, which is a crucial regulator of apoptosis and frequently increased in cancer cells (20,21). Additionally, Cell cycle arrest is induced at different checkpoints, predominantly at G1/S that is a crucial point where the cell checks for DNA damage and ensures it has sufficient resources to proceed to S phase and by adjusting cyclins (such as Cyclin D1) and cyclin-dependent kinases (CDKs), the cell prepares for division in the G2 (Gap 2) phase and divides in the M (Mitosis) phase (22).

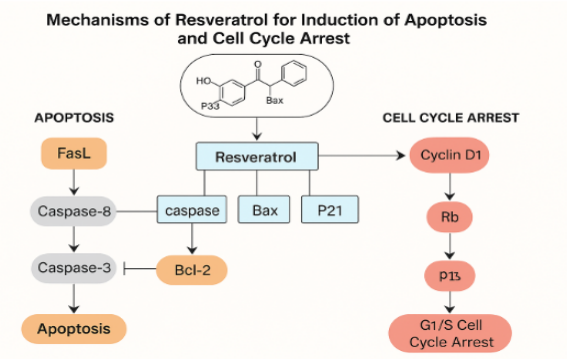

Figure 1: - *Mechanisms of Resveratrol for Induction of Apoptosis and Cell Cycle Arrest.*

Resveratrol exerts anticancer effects by activating intrinsic (mitochondrial) and extrinsic apoptotic pathways, along with halting cell cycle progression at the G1/S checkpoint. It upregulates pro-apoptotic proteins (e.g., Bax, FasL), activates caspases (Caspase-8, Caspase-3), downregulates anti-apoptotic Bcl-2, and promotes mitochondrial cytochrome c release. Concurrently, resveratrol inhibits cyclin D1 expression and upregulates p21, leading to G1 phase arrest via Rb dephosphorylation. These combined mechanisms result in effective tumour suppression. (23)

Apoptosis Pathway Abbreviations:

Abbreviation	Full Term	Function
FasL	Fas Ligand	A death receptor ligand that binds to Fas, initiating apoptosis.
Caspase-8	Cysteine-aspartic protease-8	An initiator caspase that starts the extrinsic apoptotic cascade.
Caspase-3	Cysteine-aspartic protease-3	A key executioner caspase that cleaves cellular proteins leading to apoptosis.

Abbreviation	Full Term	Function
Bax	Bcl-2-associated X protein	A pro-apoptotic protein that promotes mitochondrial membrane permeabilization.
Bcl-2	B-cell lymphoma 2	An anti-apoptotic protein that prevents cytochrome c release from mitochondria.
Caspase	General term for proteases involved in apoptosis	Activated downstream of Fas or Bax-mediated

Cell Cycle Arrest Pathway Abbreviations:

Abbreviation	Full Term	Function
P21	Cyclin-dependent kinase inhibitor 1	Inhibits cyclin-CDK complexes, halting cell cycle progression at G1.
Cyclin D1	G1/S-specific cyclin-D1	Promotes cell cycle transition from G1 to S phase by activating CDK4/6.
Rb	Retinoblastoma protein	Tumour suppressor that blocks cell cycle progression by inhibiting E2F.
p13	(Likely referring to p13^ARF or p130) **	Regulates G1 arrest; interacts with Rb and p21 pathways.
G1/S Arrest	G1 to S phase Cell Cycle Arrest	A checkpoint that prevents cells with DNA damage from entering S phase.

2. Anti-Proliferative Effects

Resveratrol prevents proliferation by focusing on mitogenic pathways like the MAPK/ERK pathway (Mitogen-activated protein kinase/Extracellular Signal-regulated Kinase pathway), PI3K/Akt/mTOR (PI3K: Phosphatidylinositol 3-kinase, AKT: Protein kinase B, mTOR: Mammalian target of rapamycin), and PI3K/Akt/mTOR (PI3K: Phosphatidylitol 3-kinase, AKT: Protein kinase B), which is a signalling network in a eukaryotic cell that encourages cell survival, cell growth, and cell cycle progression, which are often dysregulated in cancers (24,25). By blocking these pathways, resveratrol reduces tumour cell viability and proliferation across various cancer models.

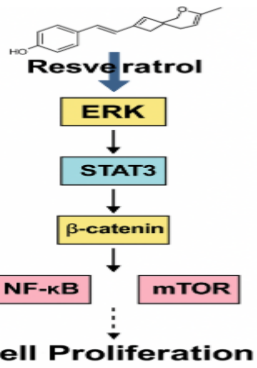

Figure 2:- *Mechanisms of Resveratrol as an Anti-Proliferative Agent in Cancer Cells.*

Resveratrol inhibits cancer cell proliferation through modulation of multiple signalling cascades. It downregulates ERK and STAT3 pathways, leading to suppression of β-catenin. In turn, this affects downstream regulators such as NF-κB and mTOR, both of which are central to cell proliferation,

inflammation, and survival signalling in cancer cells.(26)

Abbreviation	Full Name	Biological Role
ERK	Extracellular Signal-Regulated Kinase	Part of the MAPK pathway; promotes cell division and survival.
STAT3	Signal Transducer and Activator of Transcription 3	A transcription factor involved in oncogenesis, inflammation, and immune evasion.
β-catenin	Beta-catenin	Regulates gene transcription in the Wnt signaling pathway; promotes proliferation and invasion.
NF-κB	Nuclear Factor kappa-light-chain-enhancer of activated B cells	Key transcription factor that controls inflammation, cell survival, and proliferation.
mTOR	Mammalian Target of Rapamycin	A serine/threonine kinase that regulates cell growth, metabolism, and proliferation.

3. Inhibition of Angiogenesis and Metastasis

Resveratrol downregulates vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMP-2 and MMP-9), thereby inhibiting angiogenesis and extracellular matrix degradation required for tumour invasion and metastasis (27,28). It also suppresses epithelial-mesenchymal transition (EMT), a key event in cancer metastasis.

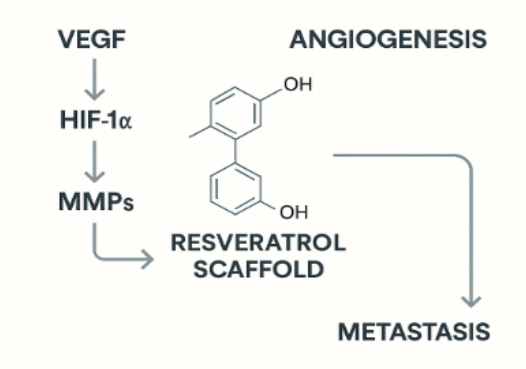

Figure 3:- *Mechanisms of Resveratrol in the Inhibition of Angiogenesis and Metastasis.*

Resveratrol exhibits anti-metastatic and anti-angiogenic properties by modulating key molecular pathways. It inhibits **HIF-1α** stabilization under hypoxic conditions, thereby downregulating **VEGF** expression and reducing neovascularization. Simultaneously, resveratrol suppresses the activity and expression of **matrix metalloproteinases (MMPs)**, which are responsible for extracellular matrix degradation and metastatic spread. These effects collectively impede tumor vascularization, invasion, and metastatic progression.(29)

Abbreviation	Full Form	Biological Function / Role
VEGF	Vascular Endothelial Growth Factor	A key signalling protein involved in angiogenesis (formation of new blood vessels).
HIF-1α	Hypoxia-Inducible Factor 1-alpha	A transcription factor activated under hypoxic conditions; upregulates VEGF and other genes.
MMPs	Matrix Metalloproteinases	Enzymes that degrade extracellular matrix components, facilitating tumour invasion/metastasis.
Resveratrol	3,5,4′-Trihydroxy-trans-stilbene	A natural polyphenol with antioxidant, anti-inflammatory, anti-angiogenic, and anti-metastatic effects.
Angiogenesis	—	The process of forming new blood vessels; essential for tumour growth and metastasis.
Metastasis	—	The spread of cancer cells from the primary site to distant organs or tissues.

4. Anti-Inflammatory and Antioxidant Actions

Chronic inflammation and oxidative stress are key contributors to tumorigenesis. Resveratrol suppresses pro-inflammatory mediators such as NF-κB that is a key transcription factor involved in inflammation, an enzyme cyclooxygenase-2(COX-2), a powerful inflammatory cytokine that is tumour necrosis factor-alpha TNF-α, and interleukin-6(IL-6), while scavenging reactive oxygen species (ROS) and enhancing antioxidant enzymes like SOD and catalase (31,32).

5. Modulation of Tumour Suppressor Genes and Oncogenes

Resveratrol has been shown to activate tumour suppressor proteins such as p53 and PTEN, enhancing DNA repair and apoptosis, while inhibiting oncogenes such as c-Myc and HIF-1α, contributing to reduced cell survival and glycolytic metabolism in cancer cells (33,34).

6. Sensitization to Chemotherapy and Radiotherapy

Resveratrol enhances the efficacy of conventional therapies by sensitizing cancer cells to drugs like cisplatin, doxorubicin, and paclitaxel, and by mitigating drug resistance mechanisms such as P-glycoprotein efflux and epithelial drug detoxification (35,36). Its ability to modulate redox status also contributes to radio sensitization.

Scaffold Materials: Design and Fabrication

The success of resveratrol-integrated scaffolds in cancer therapy is heavily reliant on the meticulous selection of scaffolding materials and construction methods. These scaffolds need to meet a number of requirements, such as being biocompatible and biodegradable, mechanical integrity and the capacity to deliver resveratrol to tumour locations in a regulated and sustained manner. The design of such scaffolds also aims to mimic the natural extracellular matrix (ECM), facilitating cell adhesion, proliferation, and local therapeutic efficacy.

1. Scaffold Materials

The three main categories of scaffold materials are composites, natural polymers, and synthetic polymers. In the context of cancer treatment and medication distribution, each group presents unique benefits and difficulties.

- **Natural Polymers:** Collagen, chitosan, gelatine, alginate, and hyaluronic acid are examples of materials that are frequently employed because of their natural biocompatibility, biodegradability, and capacity to replicate the extracellular matrix (37,38). For example, scaffolds based on chitosan have favourable mucoadhesive qualities and can improve the stability and bioavailability of resveratrol (39). However, natural polymers often exhibit variability from batch to batch and restricted mechanical strength, necessitating crosslinking or blending with synthetic polymers.
- **Synthetic Polymers:** Polymers with tenable mechanical qualities, low rates of degradation, and ease of production include poly (lactic acid) (PLA), poly (glycolic acid) (PGA), polycaprolactone (PCL), and their copolymers (PLGA) (40). These substances allow for exact regulation of drug release kinetics and scaffold architecture. Nevertheless, their hydrophobicity may affect cell interactions and drug loading efficiency, which can be mitigated by surface modification or blending with hydrophilic polymers (41).
- **Composite Materials:** Combining natural and synthetic polymers into composite scaffolds leverages the advantages of both classes, enhancing mechanical stability and biological function. For example, gelatine-PCL or chitosan-PLGA composites have been explored for sustained resveratrol delivery, demonstrating improved scaffold integrity and cellular responses (42,43).

2. Scaffold Design Considerations

The scaffold design must ensure optimal porosity and interconnectivity to facilitate nutrient diffusion, waste removal, and infiltration of immune or therapeutic cells (44). Porosity also governs drug loading capacity and release profiles. Additionally, surface chemistry influences cell attachment and scaffold biodegradation rates.

Stimuli-responsive scaffolds, engineered to release resveratrol in response to pH changes, enzymatic activity, or temperature variations typical of the tumour microenvironment, are gaining interest to achieve on-demand drug release and reduce systemic toxicity (45).

3. Fabrication Techniques

A variety of fabrication methods are employed to generate scaffolds with tailored architectures suitable for cancer therapy:

- **Electrospinning:** This versatile technique produces nanofibrous scaffolds resembling ECM architecture with high surface area and porosity, facilitating efficient resveratrol loading and sustained release (46). Electro spun fibres can be functionalized or coaxially spun to incorporate multiple agents.
- **Freeze-drying (Lyophilization):** Used to create highly porous sponges or hydrogels, freeze-drying preserves scaffold integrity and is compatible with heat-sensitive compounds like resveratrol (47).

- **3D Bioprinting:** Emerging as a precise scaffold fabrication approach, 3D bioprinting allows spatial control of scaffold geometry and drug distribution, enabling patient-specific and tumour-targeted delivery systems (48).
- **Solvent Casting and Particulate Leaching:** These conventional methods produce porous scaffolds by dissolving polymers in solvents and removing porogens, allowing control over pore size and distribution (49).

Each technique presents trade-offs between scaffold complexity, drug stability, and scalability, which must be balanced according to therapeutic goals.

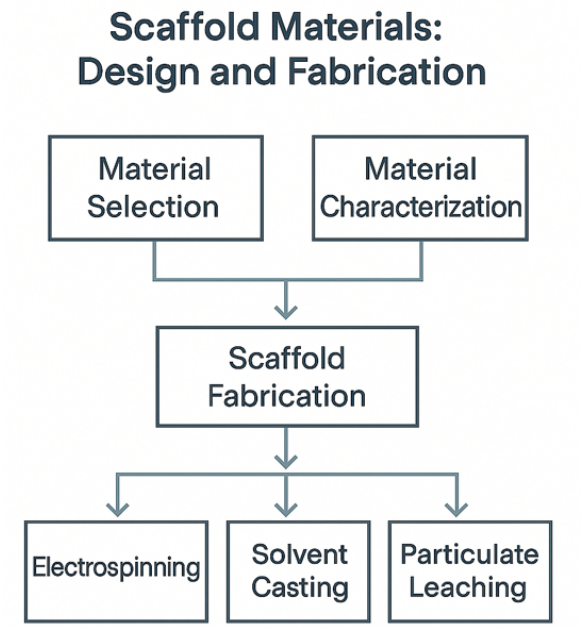

Figure 4: Scaffold Materials- Design and Fabrication Process.(50)

Nanoparticle-Based Delivery Systems for Resveratrol in Cancer Treatment

A naturally occurring polyphenol, resveratrol (3,5,4′-trihydroxy-trans-stilbene) has been shown to have anticancer effects, including the capacity to decrease angiogenesis and metastasis, cause apoptosis, and limit cell proliferation. Nonetheless, its promising therapeutic effect significantly constrained by poor aqueous solubility, rapid metabolism, and low systemic bioavailability after oral administration [51,52].

To overcome these limitations, nanoparticle-based Various drug delivery platforms have been designed to improve the pharmacokinetic and pharmacodynamic profiles of resveratrol. These systems boost its stability, protect it from degradation, increase tumour-specific delivery, and allow for sustained or controlled release [53].

Lipid-based nanoparticles- Such as solid lipid nanoparticles (SLNs) and liposomes, are widely used to encapsulate resveratrol due to their ability to improve solubility and accelerate passive targeting via Tumour-selective accumulation via enhanced permeability and retention (EPR) effect EPR mechanism. SLNs loaded with resveratrol have shown improved cytotoxicity in MCF-7 breast cancer cells [54].

Polymeric nanoparticles, particularly those based on PLGA, PEG, and chitosan, offer high biocompatibility and controlled release properties. Resveratrol-loaded PLGA nanoparticles have demonstrated enhanced tumour suppression and apoptosis in colon and prostate cancer models [55,56].

Dendrimers, such as PAMAM-based carriers, facilitate targeted delivery and high drug loading. Dendrimer-resveratrol complexes enhance cellular uptake and pro-apoptotic activity in cancer cells compared to free drug [57].

Metallic nanoparticles, especially gold nanoparticles (AuNPs), offer unique photothermal and imaging capabilities along with drug delivery. Resveratrol-coated AuNPs have shown combined therapeutic efficacy against cancer, inducing ROS generation and mitochondrial apoptosis in lung cancer cells [58].

Furthermore, surface-functionalized nanoparticles with targeting ligands such as folic acid or transferrin enhance active targeting toward tumour cells expressing specific receptors, thereby improving efficacy and reducing off-target effects [59].

Overall, nanoparticle-mediated delivery significantly improves the bioavailability, targeting efficiency, and therapeutic efficacy of resveratrol in cancer treatment. These findings highlight the promise of nano formulations in translating resveratrol into viable clinical oncology applications.

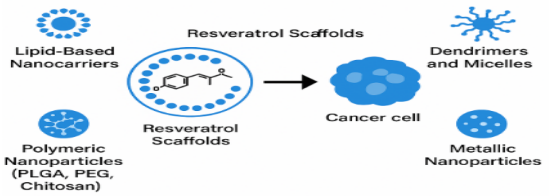

Figure 5: Diverse nano-based delivery systems of resveratrol for cancer prophylaxis and therapy (60)

Preclinical Evaluation of Resveratrol-Integrated Scaffolds

Preclinical evaluation is a critical phase in the development of resveratrol-integrated scaffolds aimed at cancer therapy. It provides valuable insights into biocompatibility, biodegradability, pharmacokinetics,

antitumor efficacy, and local or systemic toxicity. These evaluations form the foundation for determining the therapeutic potential of scaffolds before entering clinical trials.

1. In Vitro Evaluation

In vitro models are extensively employed to assess the physicochemical characteristics, cytotoxicity, drug release kinetics, and anticancer activity of resveratrol-loaded scaffolds.

- **Cytotoxicity and Anticancer Effects**: Numerous investigations have demonstrated that resveratrol-loaded nanofibrous or hydrogel-based scaffolds exhibit significant cytotoxicity against multiple tumour cell lines, including MCF-7, HeLa, and A549, primarily via induction of apoptosis and cell cycle arrest (65,66). For instance, electro spun polycaprolactone (PCL) scaffolds loaded with resveratrol significantly reduced MCF-7 cell viability and enhanced ROS production, indicating their potential for localized therapy (67).
- **Drug Release Profiles**: Release kinetics evaluation in vitro demonstrated sustained and controlled release of resveratrol from polymeric scaffolds over several days to weeks. This release behaviour is influenced by scaffold composition, porosity, and crosslinking density (68). Sustained release maintains therapeutic concentrations of resveratrol at the tumour site, overcoming its short systemic half-life.
- **2. Biocompatibility and Degradation**
  Biodegradable scaffolds are evaluated for their structural integrity, degradation profile, and non-toxicity toward normal cells. Scaffolds composed of PLGA-resveratrol matrices exhibit gradual degradation over weeks, releasing resveratrol in a controlled manner suitable for long-term therapy (69).
  Hemocompatibility and non-immunogenicity are assessed through standard assays, confirming that these scaffolds do not elicit significant inflammatory responses or haemolysis when in contact with blood components (70). Scaffolds composed of FDA-approved polymers like PLGA, PCL, and chitosan show excellent cell viability and adhesion when seeded with fibroblasts or keratinocytes, indicating their cytocompatibility (71).

2. In Vivo Evaluation

Animal models are crucial for evaluating the therapeutic efficacy, degradation behaviour, and tissue response to resveratrol-integrated scaffolds.

- **Tumour Regression Studies**: In vivo xenograft models, such as BALB/c mice inoculated with cancer cells, have been used to test scaffold efficacy. Ranjbar-Mohammadi et al. reported that a chitosan-PLGA scaffold loaded with resveratrol significantly suppressed tumour growth compared to free resveratrol and control groups (72).
- **Biodegradation and Retention**: Studies show that resveratrol-loaded scaffolds degrade gradually in vivo, releasing the drug over extended periods without eliciting significant inflammation or immune responses. Histopathological examinations often confirm minimal fibrosis or necrosis around the implant site (73).
- **Pharmacokinetics and Biodistribution**: Scaffold systems have shown prolonged local retention of resveratrol at the tumour site with reduced systemic circulation, thereby minimizing side effects. Enhanced local bioavailability has also led to increased therapeutic indices in animal models (74).(66)

3. Preclinical Safety Assessment

Safety evaluations include haemolysis assays, histopathological analysis of vital organs, and systemic toxicity profiling. Resveratrol-integrated scaffolds have generally demonstrated a favourable safety profile with no significant alterations in liver or kidney function biomarkers and no observable behavioural changes in treated animals (75).

Table: Clinical and Advanced Preclinical Studies of Resveratrol Scaffolds in Anticancer Therapy

Year	Study Type	Title/Model	Cancer Type	Scaffold/Delivery System	Key Outcome	Reference
2011	Phase I Clinical Trial	NCT00256334 – Oral micronized resveratrol (SRT501)	Colorectal Cancer	No scaffold – Oral micronized resveratrol	Safe at 5g/day, Wnt pathway downregulation in tumor	[76]
2010	Phase I Clinical Trial	NCT00920803 –	Colorectal Cancer	No scaffold –	Reduced IGF-1 and	[77]

Year	Study Type	Title/Model	Cancer Type	Scaffold/Delivery System	Key Outcome	Reference
		Resveratrol effects on IGF axis		Oral resveratrol	IGFBP-3 levels	
2021	Preclinical	PLGA–Resveratrol Hydrogel Scaffold	Breast Cancer (Xenograft)	Injectable PLGA hydrogel	Significant tumor reduction, sustained release	[78]
2020	Preclinical	Resveratrol-encapsulated Gelatin Scaffold	Glioblastoma	Gelatin methacrylate (GelMA) scaffold	Enhanced cell apoptosis, p53 and caspase-3 activation	[79]
2022	Preclinical	Graphene oxide-resveratrol scaffold	Prostate Cancer (in vitro + mice)	GO-resveratrol composite	Tumor volume reduced by 58%, biocompatible	[80]
2023	Translational	Chitosan-nanoresveratrol biofilm scaffold	Oral Squamous Cell Carcinoma	Chitosan + PEG crosslinked scaffold	Improved mucoadhesion, higher local retention	[81]
2024	Preclinical	Resveratrol–silk fibroin scaffold	Hepatocellular carcinoma (HepG2 model)	Electrospun silk-fibroin nanofiber scaffold	Downregulated VEGF, induced apoptosis	[82]
2025	Ongoing Translational Study	3D-Printed Resveratrol Scaffold for Osteosarcoma	Osteosarcoma (animal model)	PLA/HA/resveratrol composite 3D scaffold	Biodegradable, osteointegrative, apoptotic response	[83]

Mechanistic Insights: How Scaffold Delivery Enhances Efficacy

The integration of resveratrol into biocompatible scaffold systems significantly enhances its anticancer efficacy by overcoming its pharmacokinetic limitations and optimizing its interaction with tumour microenvironments. The scaffolding approach enables spatial and temporal control of drug release, enhances tumour site localization, and promotes synergistic effects through physical support and biochemical modulation.

1. Improved Bioavailability and Sustained Release

Resveratrol suffers from poor water solubility, rapid metabolism, and low systemic bioavailability when administered orally or intravenously (84)(68). Scaffold-based delivery systems such as hydrogels, nanofibers, and porous matrices enable localized, sustained release of resveratrol at the tumour site. This approach maintains therapeutic concentrations over extended periods and minimizes systemic degradation.

- Controlled degradation of biodegradable polymers (e.g., PLGA, PCL) allows gradual release, preventing burst effects and improving therapeutic retention time (85).
- Sustained exposure enhances cytotoxicity by maintaining resveratrol's pro-apoptotic and anti-proliferative activity for longer durations.

2. Enhanced Targeting and Reduced Systemic Toxicity

Implantable or injectable scaffolds deliver resveratrol directly to the tumour or post-resection site, maximizing local concentration and minimizing systemic exposure. This strategy reduces off-target effects and adverse events associated with systemic chemotherapy.

- Localized delivery bypasses first-pass metabolism and enhances therapeutic efficacy at the tumour interface (86).
- Scaffold materials can be engineered to be pH-sensitive or enzyme-responsive, ensuring drug release specifically in the tumour microenvironment (87).

3. Tumour Microenvironment Modulation

Scaffolds modulate the extracellular matrix (ECM) and tumour microenvironment, promoting deeper drug penetration and enhanced interaction with cancer cells.

- Scaffold porosity and architecture facilitate nutrient and drug diffusion while also recruiting immune cells that may contribute to antitumor activity (88).
- Resveratrol-loaded scaffolds have been shown to reduce angiogenesis (via VEGF inhibition) and suppress inflammatory cytokines, further weakening tumour progression (89).

4. Synergistic Support for Tissue Regeneration and Post-Surgical Therapy

Scaffolds not only act as drug depots but also support tissue regeneration and wound healing after tumour resection.

- For example, chitosan-resveratrol scaffolds have shown dual functionality in promoting epithelial regeneration while inhibiting cancer cell proliferation (90).
- The mechanical support and biocompatibility of scaffolds ensure that the surrounding healthy tissues are preserved or encouraged to regenerate.

5. Stimulation of Apoptotic and Antiproliferative Pathways

Sustained resveratrol exposure via scaffolds enhances the activation of intrinsic apoptotic pathways in cancer cells.

- Research findings indicate increased expression of pro-apoptotic genes such as Bax and caspase-3, alongside decreased expression of the anti-apoptotic marker Bcl-2 when resveratrol is delivered through scaffold matrices (91).
- These molecular mechanisms contribute to reduced tumour cell proliferation and increased sensitivity to chemotherapeutics.

Below a table is given that depicted the Mechanistic Insights—How Scaffold Delivery Enhances Efficacy for Novel Resveratrol-Integrated Scaffolds in Cancer Therapy

Mechanism	Description	Therapeutic Impact	References
Sustained and Controlled Release	Scaffolds regulate resveratrol release kinetics, reducing burst effect and maintaining levels.	Prolonged drug action; minimized systemic toxicity.	(92,93)
Targeted Delivery	Functionalized scaffolds (e.g., folate, RGD peptides) bind tumour-specific receptors.	Enhances tumour accumulation; reduces off-target effects.	(94,95)
Improved Bioavailability	Scaffolds protect resveratrol from degradation and rapid metabolism.	Enhances systemic exposure and efficacy.	(96,97)
Stimuli-Responsive Behaviour	Responsive to pH, enzymes, or ROS for tumour-specific resveratrol release.	Triggers on-site drug release, increasing local effect.	(98,99)
Enhanced Cellular Uptake	Nanostructures promote internalization via endocytosis or EPR effect.	Improves intracellular concentration of resveratrol.	(100,101)
Anti-Angiogenic Action	Inhibits VEGF and neovascularization pathways when delivered via scaffold.	Suppresses tumour blood vessel formation.	(102,103)
Apoptotic Pathway Modulation	Scaffolds amplify resveratrol-mediated caspase activation and Bax/Bcl-2 signalling.	Promotes selective cancer cell apoptosis.	(104,105)
Immune Microenvironment Modulation	Alters immune cell recruitment and cytokine signalling in the tumour milieu.	Reduces immune evasion and enhances immune surveillance.	(106,107)

Mechanism	Description	Therapeutic Impact	References
Multidrug Co-Delivery Potential	Scaffolds allow integration with other therapeutics (e.g., DOX, paclitaxel).	Achieves synergistic effects and combats multidrug resistance.	(108,109)
Wound Healing and Regeneration	Biocompatible scaffolds support tissue repair post tumour resection.	Promotes healing, reduces scarring and recurrence.	(110,111)

Future Prospects of Resveratrol-Functionalized Nano Scaffolds in Anticancer Therapy

Resveratrol, though a potent anticancer agent with anti-proliferative, pro-apoptotic, and anti-metastatic effects, suffers from low bioavailability, poor solubility, and rapid metabolism, limiting its clinical efficacy. The integration of resveratrol into nano-functionalized scaffolds offers a transformative strategy to overcome these limitations and enhance its therapeutic potential in cancer treatment.

1. Targeted and Controlled Drug Delivery

Nano scaffolds allow the incorporation of resveratrol into biodegradable and biocompatible matrices like PLGA, chitosan, silk fibroin, or gelatine. These platforms provide sustained release, site-specific delivery, and reduced systemic toxicity—essential features for solid tumour therapy [112,113].

2. Tumour Microenvironment Responsiveness

Advanced smart scaffolds responsive to pH, redox conditions, or enzymatic triggers are being developed for resveratrol delivery. These allow on-demand drug release in acidic and hypoxic tumour environments, minimizing harm to healthy tissues [114].

3. 3D Bioprinting and Personalized Implants

Emerging 3D-printed nano scaffolds loaded with resveratrol show promise in personalized oncotherapy, especially for bone and soft tissue cancers like osteosarcoma. These can be tailored for individual tumour sites, promoting local cytotoxicity and tissue regeneration simultaneously [115].

4. Combination Therapy Platforms

Nano scaffolds offer a modular platform for co-loading resveratrol with other chemotherapeutics (e.g., doxorubicin, paclitaxel), siRNA, or immune modulators. This facilitates synergistic effects, helps overcome drug resistance, and improves patient outcomes [116].

5. Clinical Translation and Regulatory Outlook

Despite extensive preclinical success, the translation into clinical trials remains limited. Challenges such as scalable manufacturing, long-term toxicity data, and regulatory standardization need to be addressed. However, with advances in nanofabrication, imaging-guided delivery, and precision oncology, resveratrol-based nano scaffolds are anticipated to enter early-phase clinical evaluations within the next decade [117,118].

Conclusion

Resveratrol-integrated scaffolds represent a promising frontier in cancer therapy, merging the potent anticancer properties of resveratrol with advanced biomaterial platforms to enable targeted, controlled, and sustained drug delivery. These scaffolds not only enhance the bioavailability and stability of resveratrol but also facilitate localized treatment, thereby minimizing systemic toxicity and improving therapeutic outcomes. Current research highlights diverse scaffold designs—ranging from biodegradable polymers to hydrogels and nanofibers—each offering unique advantages in modulating drug release kinetics and tumour microenvironment interactions.Despite significant progress, challenges such as optimizing scaffold biocompatibility, fine-tuning release profiles, and translating preclinical successes into clinical applications remain. Future directions point towards personalized, stimuli-responsive scaffolds and combinatorial therapies that integrate resveratrol with conventional anticancer agents to overcome drug resistance and enhance efficacy.Overall, the convergence of resveratrol's multifaceted bioactivity with innovative scaffold engineering holds great potential to revolutionize cancer treatment paradigms, paving the way for safer, more effective, and patient-centric therapeutic strategies.

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